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IN RE APPLICATION OF: Lorena MUGGETTI, et al.

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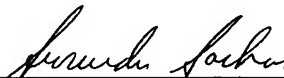
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INTERNATIONAL FILING DATE: August 3, 2000

FOR: FORMULATIONS FOR PARENTERAL USE OF ESTRAMUSTINE PHOSPHATE WITH  
IMPROVED PHARMACOLOGICAL PROPERTIES**REQUEST FOR PRIORITY UNDER 35 U.S.C. 119  
AND THE INTERNATIONAL CONVENTION**Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that  
the applicant claims as priority:**COUNTRY**  
Great Britain**APPLICATION NO**  
9921954.5**DAY/MONTH/YEAR**  
16 September 1999Certified copies of the corresponding Convention application(s) were submitted to the  
International Bureau in PCT Application No. PCT/EP00/07679. Receipt of the certified  
copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been  
acknowledged as evidenced by the attached PCT/IB/304.Respectfully submitted,  
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1. Your reference

P.77586 GCW.CMK

2. Patent application number

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16 SEP 1999

3. Full name, address and postcode of the or of each applicant (underline all surnames)

PHARMACIA & UPJOHN S.P.A.

Via Robert Koch 1.2  
20152 Milan  
Italy

Patents ADP number (if you know it)

7100001001

If the applicant is a corporate body, give the country/state of its incorporation

Italy

4. Title of the invention

FORMULATIONS FOR PARENTERAL USE OF  
ESTRAMUSTINE PHOSPHATE WITH IMPROVED  
PHARMACOLOGICAL PROPERTIES.

5. Name of your agent (if you have one)

J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

14 SOUTH SQUARE  
GRAY'S INN  
LONDON WC1R 5LX

Patents ADP number (if you know it)

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Number of earlier application

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer "Yes" if:

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  - b) there is an inventor who is not named as an applicant, or
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Description 12

Claim(s) 4

Abstract 1



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Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application

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12. Name and daytime telephone number of person to contact in the United Kingdom Mrs C M Keen  
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FORMULATIONS FOR PARENTERAL USE OF ESTRAMUSTINE PHOSPHATE  
WITH IMPROVED PHARMACOLOGICAL PROPERTIES

5

The present invention relates to pharmaceutical  
formulations of estramustine phosphate for parenteral use  
with improved pharmacological properties and, more  
particularly, to formulations of estramustine phosphate for  
10 parenteral use further comprising sulfoalkyl ether  
cyclodextrins and human albumin.

Estramustine phosphate (The Merck Index, XII Ed., No. 3749,  
1996) is an estradiol-17 $\beta$ -phosphate derivative widely known  
15 in the art as antitumor agent, currently used in the  
treatment of advanced adenocarcinoma of the prostate.

The drug is usually administered orally; preferably at a  
dose of 10-15 mg/kg/day. Intravenous administration,  
however, is also adopted in some particular cases.

20 For example, initial intravenous administration of  
estramustine phosphate, followed by oral administration,  
has been reported at dosages paralleling the oral  
administration for the drug, i.e. 300-600 mg daily given  
intravenously and usually repetitively over for several  
25 consecutive days (see, for a reference, British Journal of  
Urology, 1977, 49, 73-79; J. Urol. 108:303-306, 1972; Eur.  
Clin. Pharmacol. 26(1), 113-119, 1984; Eur. Urol. 1990, 17,  
216-218).

30 Estramustine phosphate as well as other well-known  
cytotoxic compounds used in antitumor therapy are known to  
cause, or potentially cause, vascular damages at the site  
of injection when parenterally, in particular  
intravenously, administered.

35 As an example, studies in patients treated with  
estramustine phosphate administered as a slow intravenous  
injection or as a bolus, at 300 mg/day, revealed

thrombophlebitis and local irritations at the peripheral intravenous injection sites.

These drawbacks are considered major limitations for the intravenous administration of estramustine phosphate, thus requiring, in many patients, the establishment of central line administration or, in some cases, even discontinuation of the treatment.

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With the aim of minimising the unwanted effects associated with the intravenous administration of cytotoxic agents, a few means are reported in the art.

Among them is the use of cyclodextrins, for instance hydroxypropyl-cyclodextrin, in the preparation of formulations for parenteral administration of cytotoxic known to cause ulcerative lesions. See, for a reference, US patent No. 5,804,568 in the name of Supergen Inc.

Cyclodextrin derivatives such as sulfoalkyl ether cyclodextrins are known in the art as solubilizing agents for insoluble or poorly soluble drugs (see, for a reference, US 5,134,127 in the name of the University of Kansas).

Also known in the art are formulations for the intravenous administration of estramustine phosphate containing human albumin, reported to be characterised by fewer local side-effects upon injection of the active (see, for a reference, H. Schutz et al.; Krankenhauspharmazie, II year, issue No. 3, 1988).

In this respect, we found formulations for parenteral use comprising estramustine phosphate together with sulfoalkyl ether cyclodextrins and human albumin which, unexpectedly, resulted to achieve optimal protection from side-effects associated with estramustine administration.

It is therefore the object of the present invention a formulation for parenteral use comprising estramustine phosphate in admixture with a sulfoalkyl ether cyclodextrin and human albumin.



Once administered intravenously to patients, the formulations object of the present invention do not provoke ulcerative damages, nor thrombophlebitis, at the site of  
5 injection.

Very interestingly, the estramustine phosphate formulations of the invention result to be endowed with unexpected  
pharmacological properties, expressed in terms of toxicity  
at the site of injection, markedly improved with respect to  
10 formulations containing, as a single protective excipient, a sulfoalkyl ether cyclodextrin or, alternatively, human albumin.

In the present invention, unless otherwise specified, with  
15 the term formulation comprising estramustine phosphate, as the active ingredient, we intend any formulation comprising estramustine phosphate either in the acid form or as a pharmaceutically acceptable salt for parenteral administration such as, for instance, a salt with a basic  
20 amino acid or with N-methyl glucamine, otherwise referred to as meglumine.

Preferably, estramustine phosphate is in the form of its meglumine salt.

With the term sulfoalkyl ether cyclodextrin we refer to any  
25 cyclodextrin of the above type wherein alkyl stands for straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl group such as methyl, ethyl, n.propyl, isopropyl, n.butyl, isobutyl, sec-butyl, tert-butyl, n.pentyl, n.hexyl and the like.

Preferably, the formulation of the present invention  
30 comprises estramustine phosphate in admixture with sulfobutyl ether  $\beta$ -cyclodextrin.

According to a preferred embodiment of the invention, the weight ratio between estramustine phosphate and sulfoalkyl  
35 ether cyclodextrin is comprised from about 1:0.5 to about 1:5, respectively.

However, higher amounts of sulfoalkyl ether cyclodextrin with respect to the active are still effective and hence comprised within the scope of the present invention.

- 5 According to another preferred embodiment of the invention, the above formulations are advantageously used for intravenous use.

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As such, these formulations of the invention can be administered to patients either as a slow injection, e.g.  
10 over about 30 minutes to about 3 hours, or as a bolus injection, also referred to as IV (intravenous) push.

- In another preferred embodiment of the invention either  
(i) the estramustine phosphate is in lyophilised form and  
15 the parenterally acceptable carrier or diluent is a physiological solution for parenteral use containing the sulfoalkyl ether cyclodextrin and the human albumin, or  
(ii) the estramustine phosphate and sulfoalkyl ether  
20 cyclodextrin are in lyophilised form and the parenterally acceptable carrier or diluent is a physiological solution for parenteral use containing the human albumin.

- 25 The invention also provides a product which comprises estramustine phosphate in lyophilised form and a physiological solution for parenteral use containing human albumin.

- 30 The formulations of the invention also provide a very advantageous method for delivering estramustine phosphate intravenously, even when high doses of the active are needed.

- It is therefore a further object of the invention a  
35 formulation for parenteral use comprising estramustine phosphate, as a single infusion dosage of the active exceeding 1300 mg, in admixture with a sulfoalkyl ether cyclodextrin and human albumin.

According to another preferred embodiment of the invention, it is further provided a formulation for parenteral use comprising estramustine phosphate, as a single infusion dosage of the active exceeding 950 mg/m<sup>2</sup>, in admixture with a sulfoalkyl ether cyclodextrin and human albumin.

The formulations object of the present invention allow the administration of the active either as a single agent or, alternatively, according to a combined chemotherapy regimen.

As an example, the above formulations can be administered in combination with one or more chemotherapeutic agents such as, for instance, taxane, taxane derivatives, CPT-11, camptothecin derivatives, anthracycline glycosides, e.g. doxorubicin or epirubicin, etoposide, navelbine, vinblastine, carboplatin, cisplatin and the like, optionally within liposomal formulations thereof.

Therefore, it is a further object of the present invention a product containing a formulation for parenteral use of estramustine phosphate in admixture with a sulfoalkyl ether cyclodextrin and human albumin and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

25

### Toxicology

To study the local irritant effects of estramustine phosphate after repeated intravenous administrations to rats, in comparison to a formulation of estramustine phosphate according to the present invention, the active was dissolved in different vehicles such as water solution for injection and water solution for injection further containing sulfobutyl ether  $\beta$ -cyclodextrin and human albumin. In addition, formulations of estramustine phosphate in admixture with sulfobutyl ether  $\beta$ -cyclodextrin only or, alternatively, with human albumin only, were used for comparison.

In particular, the following water for injection solutions wherein either the active estramustine phosphate (therein referred to as EMP) as well as the excipients sulfobutyl ether  $\beta$ -cyclodextrin and human albumin (therein referred to as SBECD and HA, respectively) are expressed in terms of weight ratios, were prepared and tested:

- 
- |    |                       |                        |
|----|-----------------------|------------------------|
|    | (a) negative control: | water for injection;   |
|    | (b) positive control: | EMP;                   |
| 10 | (c) comparison:       | EMP:SBECD=1:1;         |
|    | (d) comparison:       | EMP:HA=1:0.21;         |
|    | (e) tested solution:  | EMP:SBECD:HA=1:1:0.21; |

Male Sprague-Dawley rats were used because of their acceptance as a predictor of toxic change in man. The rats were 6 weeks old at the start of the study.

Estramustine phosphate, in the form of meglumine salt, was administered to groups of rats as a repeated intravenous injection during 3 days. Rats were then sacrificed: a half of the rats at the fourth day and a half at the fifth day. The dose level of estramustine phosphate, in all the different tested solutions, was of 150 mg/kg/day.

Clinical observations were recorded daily. Thrombophlebitic side effects resulted in a dark bluish/blackish coloration of the tail during the treatment period.

A score system based on tail coloration and its extension was used to evaluate the different tested formulations.

The score system considered estramustine phosphate water solution (b) as the positive control (i.e. marked toxicity). Water for injection (a) was administered to the control group as negative control (i.e. no toxicity signs). Histological evaluation was carried out on the tail of the rats treated with the composition of the invention.

Estramustine phosphate in a water solution (b) induced, at the used dose, local irritant effects at the injection site

after the first administration and marked toxicity signs at the end of the experiment.

Likewise, toxicity signs at the injection site were also observed for the comparison (c) and (d) EMP solutions

5 containing SBECD or HA, as the sole excipients.

On the contrary, no toxicity was observed with the formulation of the invention containing sulfobutyl ether  $\beta$ -cyclodextrin and human albumin (e).

10 Moreover, histological evaluation of the tail of the rats treated with the formulation (e) did not reveal any damage when compared to the tails of the control group.

In addition, the synergistic protective effect exerted by combining both SBECD and HA excipients, as per the invention, can clearly be evidenced by considering the  
15 formulation of the invention (e) in comparison to the formulations (c) and (d) wherein each single excipient is present in the same amount with respect to the active.

It was thus concluded that estramustine phosphate in a  
20 water solution containing sulfoalkyl ether cyclodextrin and human albumin, according to the present invention, induced markedly less local irritant effects when compared with a water solution of estramustine phosphate itself.

Even more surprisingly, the formulation of the invention  
25 produced less local irritant effects also in comparison to analogous solutions of estramustine phosphate containing sulfoalkyl ether cyclodextrin only or human albumin only.

One particularly preferred schedule for administering the  
30 formulation of estramustine phosphate according to the invention is a single infusion given once weekly to a maximal dose of 4000 mg or 3500 mg/m<sup>2</sup>.

Another preferred schedule is the administration of a single drug infusion once every two to four weeks.

One schedule may be preferred over another in consideration of schedules with other optional concomitant therapy. These schedules may repeat in serial or as repetitive fashion.

- 5 The formulations of the present invention are useful in antitumor therapy, particularly in the treatment of prostate cancer, breast cancer, melanoma, lung cancer,  
pancreatic cancer, colorectal cancer, ovarian cancer and cancers of the brain.

10

The formulations object of the present invention are prepared according to conventional techniques adopted in the preparation of pharmaceutical forms for parenteral use. Typically, a proper amount of estramustine phosphate,  
15 either as a dry powder or into a lyophilised form, is dissolved in a pharmaceutically acceptable solution for parenteral use and then admixed with a proper amount of a sulfoalkyl ether cyclodextrin, for instance sulfobutyl ether  $\beta$ -cyclodextrin.

- 20 The above solution is then admixed with a proper amount of human albumin, either as a dry powder or as a commercially available solution, e.g. human albumin 25%, 20% or 5%, optionally properly diluted.

- As an example, a proper amount of estramustine phosphate in  
25 the form of a suitable salt such as, for instance, N-methyl glucamine salt, is dissolved in a suitable amount of sterile water or aqueous dextrose solution, e.g. 5% dextrose in water for intravenous administration, and then admixed with a proper amount of powdered sulfobutyl ether  
30  $\beta$ -cyclodextrin.

The above admixture is subsequently added with a proper amount of human albumin, for instance as a dry powder, and subsequently stirred, sterilised and lyophilised according to conventional techniques.

- 35 From the foregoing it is clear to the man skilled in the art that each of the excipients of the invention, namely sulfoalkyl ether cyclodextrin and human albumin, each independently as a powder or into a suitable solution, can

be admixed in any order to the active, already dissolved into a proper solution or in the form of a dry powder.

Likewise, the formulations of the invention can also be prepared by admixing the active with the aforementioned excipients already properly combined as above indicated.

The final freeze-dried formulation is then prepared and stored in vials for injection; the addition of a proper amount of sterile water or a physiological solution for parenteral use enables the preparation of the final formulation to be injected.

The above method is also suitable for preparing high dosages estramustine phosphate formulations whilst maintaining the desired weight ratio between the components.

The unit strength of the formulation to be injected depended on the concentration of the active in the solution itself and, of course, on the filling volume of the vials used to prepare the final formulation.

Additionally, the formulations of the present invention may optionally contain pharmaceutically acceptable excipients for parenteral administration such as, for instance, bulking agents, e.g. lactose or mannitol, pH buffering agents, anti-oxidant agents, preservative agents, tonicity adjusters and the like.

The following examples are herewith intended to better illustrate the present invention without representing any limitation to it.

#### Example 1

Preparation of estramustine phosphate N-methyl glucamine salt in admixture with sulfobutyl ether  $\beta$ -cyclodextrin (estramustine phosphate:sulfobutyl ether  $\beta$ -cyclodextrin=1:1 weight ratio)

300 mg of estramustine phosphate were weighed in a beaker and dispersed by means of magnetic stirring in 5 ml of

water. 120.8 mg of N-methyl-glucamine were then added under stirring to the watery dispersion of the active and, after a few minutes, a clear solution was obtained. 312.5 mg of sulfobutyl ether  $\beta$ -cyclodextrin were added, maintaining the solution under stirring till the solubilization was completed.

The solution obtained was then brought to the final volume of 10 ml with water so as to reach a final concentration of 30 mg/ml of estramustine phosphate and 31.25 mg/ml of sulfobutyl ether  $\beta$ -cyclodextrin (1:1 weight ratio - 1:0.25 molar ratio respectively).

A solution prepared as previously described, properly sterilized by filtration, was tested for its local vein tolerability in rats.

#### Example 2

The formulation described in Example 1 was also prepared by solubilization of the commercially available Estracyt<sup>®</sup> freeze-dried formulation containing 300 mg/vial of the active. The reconstitution of the formulation was made using 10 ml of a 31.25 mg/ml sulfobutyl ether  $\beta$ -cyclodextrin solution so as to obtain a final concentration of 30 mg/ml of estramustine phosphate and 31.25 mg/ml of cyclodextrin (1:1 weight ratio - 1:0.25 molar ratio respectively).

#### Example 3

Preparation of estramustine phosphate N-methyl glucamine salt in admixture with human albumin (estramustine phosphate:albumin=1:0.21 weight ratio)

300 mg of estramustine phosphate were weighed in a beaker and dispersed by means of magnetic stirring in 5 ml of water. 120.8 mg of N-methyl-glucamine were then added under stirring to the watery dispersion of the active and, after a few minutes, a clear solution was obtained. 0.250 ml of a commercially available solution of human albumin at 25%



concentration were added whilst maintaining the solution under stirring.

The obtained solution was then brought to the final volume of 10 ml with water so as to reach a final concentration of 30 mg/ml of estramustine phosphate and 6.25 mg/ml of human albumin (1:0.21 weight ratio respectively).

A solution prepared as previously described, properly sterilized by filtration, was tested for its local vein tolerability in rats.

10

#### Example 4

The formulation described in Example 3 was also prepared by solubilization of the commercially available Estracyt<sup>®</sup> freeze-dried formulation containing 300 mg/vial of the active. The reconstitution of the formulation was made by using 10 ml of a 6.25 mg/ml human albumin solution so as to obtain a final concentration of 30 mg/ml of estramustine phosphate and 6.25 mg/ml of human albumin (1:0.21 weight ratio respectively).

The albumin solution could be prepared either by dissolving in water a proper amount of human albumin as a dry powder or by properly diluting a commercially available human albumin solution.

25

#### Example 5

Preparation of estramustine phosphate N-methyl glucamine salt in admixture with sulfobutyl ether  $\beta$ -cyclodextrin and human albumin (estramustine phosphate:sulfobutyl ether  $\beta$ -cyclodextrin:albumin=1:1:0.21 weight ratio, respectively).

300 mg of estramustine phosphate were weighed in a beaker and dispersed by means of magnetic stirring in 5 ml of water. 120.8 mg of N-methyl-glucamine were then added under stirring to the watery dispersion of the active and, after a few minutes, a clear solution was obtained. 312.5 mg of sulfobutyl ether  $\beta$ -cyclodextrin were added, maintaining the solution under stirring until complete dissolution.

0.250 ml of a commercially available solution of human albumin at 25% concentration were then added, maintaining the solution under stirring.

5 The solution was then brought to the final volume of 10 ml with water so as to reach a final concentration of 30 mg/ml of estramustine phosphate, 31.25 mg/ml of sulfobutyl ether  $\beta$ -cyclodextrin and 6.25 mg/ml of human albumin. The weight ratio between the components of the solution were as follows: estramustine phosphate:sulfobutyl ether  $\beta$ -cyclodextrin:human albumin 1:1:0.21 respectively.

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10 A solution prepared as previously described, properly sterilized by filtration, was tested for its local vein tolerability in rats.

15 **Example 6**

The formulation described in Example 4 was also prepared by solubilization of the commercially available Estracyt<sup>®</sup> freeze-dried formulation containing 300 mg/vial of the active. The reconstitution of the formulation was made by using 10 ml of a solution containing 31.25 mg/ml of sulfobutyl ether  $\beta$ -cyclodextrin and 6.25 mg/ml of human albumin so as to reach a final concentration of 30 mg/ml of the active. The weight ratio between the components of the solution were as follows: estramustine phosphate:sulfobutyl ether  $\beta$ -cyclodextrin:human albumin 1:1:0.21 respectively.

20

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## CLAIMS

1. A pharmaceutical formulation which comprises a parenterally acceptable carrier or diluent,  
5 estramustine phosphate, a sulfoalkyl ether cyclodextrin and human albumin.

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2. A formulation according to claim 1 wherein the weight  
10 ratio of estramustine phosphate to the sulfoalkyl ether cyclodextrin is from about 1:0.5 to about 1:5.
3. A formulation according to claim 1 or 2 which is in  
15 single infusion dosage form comprising at least 1300 mg, of the estramustine phosphate.
4. A formulation according to any one of the preceding  
claims which is in single infusion dosage form  
20 comprising at least 950 mg/m<sup>2</sup>, of the estramustine phosphate.
5. A formulation according to any one of the preceding  
claims wherein the sulfoalkyl ether cyclodextrin is a  
25 straight or branched C<sub>1</sub>-C<sub>6</sub> sulfoalkyl ether cyclodextrin.
6. A formulation according to claim 5 wherein the  
sulfoalkyl ether cyclodextrin is sulfobutyl ether  $\beta$ -  
cyclodextrin.
- 30 7. A formulation according to any one of the preceding  
claims for intravenous use.
8. A formulation according to any one of the preceding  
35 claims wherein the estramustine phosphate is in the  
form of a pharmaceutically acceptable salt for  
intravenous use.

9. A formulation according to claim 8 wherein the estramustine phosphate is in the form of N-methyl glucamine salt.
- 5 10. A formulation according to any one of the preceding claims for use in the treatment of cancer.
- 
- 10 11. A formulation as claimed in claim 10 wherein the cancer is prostate cancer, breast cancer, melanoma, lung cancer, pancreatic cancer, colorectal cancer, ovarian cancer or cancer of the brain.
- 15 12. A formulation according to claim 1 wherein the estramustine phosphate is in admixture with the sulfoalkyl ether cyclodextrin and the human albumin.
- 20 13. A formulation according to claim 1 wherein  
(i) the estramustine phosphate is in lyophilised form and the parenterally acceptable carrier or diluent is a physiological solution containing the sulfoalkyl ether cyclodextrin and the human albumin, or  
(ii) the estramustine phosphate and sulfoalkyl ether cyclodextrin are in lyophilised form and the parenterally acceptable carrier or diluent is a physiological solution containing the human albumin.
- 25 14. A product which comprises  
(i) a pharmaceutical formulation which comprises a parenterally acceptable carrier or diluent and estramustine phosphate in admixture with a sulfoalkyl ether cyclodextrin and human albumin, and  
(ii) one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.
- 30 15. A product according to claim 14 wherein the sulfoalkyl ether cyclodextrin is sulfobutyl ether  $\beta$ -cyclodextrin.
- 35

16. A product according to claim 14 or 15 wherein the  
chemotherapeutic agent is selected from taxane, taxane  
derivatives, CPT-11, camptothecin derivatives,  
5 doxorubicin, epirubicin, etoposide, navelbine,  
vinblastine, carboplatin and cisplatin.

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17. A product according to claim 14 for intravenous use.

10 18. A product according to claim 14 for use in the  
treatment of prostate cancer, breast cancer, melanoma,  
lung cancer, pancreatic cancer, colorectal cancer,  
ovarian cancer or cancer of the brain.

15 19. A formulation as defined in claim 7 for use in  
suppressing or reducing the side-effects associated  
with the intravenous administration of estramustine  
phosphate and pharmaceutically acceptable salts  
thereof.

20

20. A formulation according to claim 19 wherein the side  
effects comprise ulcerative lesions and  
thrombophlebitis at the site of injection.

25 21. A product which comprises estramustine phosphate in  
lyophilised form and a physiological solution for  
parenteral use containing a sulfoalkyl ether  
cyclodextrin and human albumin.

30 22. A product which comprises estramustine phosphate and  
sulfoalkyl ether cyclodextrin in lyophilised form and a  
physiological solution for parenteral use containing  
human albumin.

35 23. Use, in the manufacture of a medicament for parenteral  
administration, of estramustine phosphate in admixture  
with a sulfoalkyl ether cyclodextrin and human albumin.

24. Use according to claim 23 wherein the medicament is for intravenous administration.

## ABSTRACT

FORMULATIONS FOR PARENTERAL USE OF ESTRAMUSTINE PHOSPHATE  
WITH IMPROVED PHARMACOLOGICAL PROPERTIES

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A pharmaceutical formulation which comprises a parenterally acceptable carrier or diluent, estramustine phosphate, a sulfoalkyl ether cyclodextrin and human albumin. The

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10 formulation can be administered according  
according to a combined chemotherapy regimen in association with one or more chemotherapeutic agents. The formulation also enables the estramustine phosphate to be administered with no side effects at the site of injection.

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